Jurnal Aisyah: Jurnal Ilmu Kesehatan

Volume 8, Issue 2, June 2023, p. 153–158
ISSN 2502-4825 (print), ISSN 2502-9495 (online)

The association of serum 25-hydroxyvitamin D and Alzheimer's Disease: A meta-analysis

Siti Sarahdeaz Fazzaura Putri[1], Irfannuddin[1*)], Krisna Murti[1], Yudianita Kesuma[1], Hardi Darmawan[1], Noriyuki Koibuchi[2 3]

[1] Faculty of Medicine, Universitas Sriwijaya
[2] Department of Integrative Physiology, Gunma University Graduate School of Medicine

ARTICLE INFO

Article history:

Received 21 November 2022
Accepted 1 April 2023
Published 10 June 2023

Keyword:

25-hydroxyvitamin D
Alzheimer's disease
meta-analysis

**) corresponding author*

Irfannuddin

Faculty of Medicine, Universitas Sriwijaya
Gedung FK Unsri, Jalan Dr. M. Ali Komplek RSMH,
Palembang, 30126, Indonesia

Email: irfannuddin@unsri.ac.id
DOI: 10.30604/jika.v8i2.1769

A B S T R A C T

Serum 25-hydroxyvitamin D deficiency has been suggested as a promising prognostic factor for dementia. Meta-analysis published revealed statistically significant differences of 25-hydroxyvitamin D levels in patients with Alzheimer's disease (AD) but other studies have been published since then.The purpose of present study was to quantify the association of serum 25-hydroxyvitamin D and AD. Literature search was performed from inception up to November 22 using Pubmed database. Based on the pooled analysis, patients with Alzheimer's disease tend to have a vitamin D deficiency relative to patients with normal cognitive function. These results strongly support the involvement of vitamin D as a critical disease-modifying variable in the reduction of AD symptoms.

INTRODUCTION

Alzheimer's disease (AD) is an age-related neurodegenerative disease that is the leading cause of dementia (Cortes-Canteli & Iadecola, 2020). Dementia is a type of brain diseases in which the deterioration of brain cells effects in memory, thought, analysis, language, and other nerve activity malfunction (Pentkowski, Rogge-Obando, Donaldson, Bouquin, & Clark, 2021)(Pentkowski et al., 2021)(Long & Holtzman, 2019) . This dysfunction can alter a behavior and personality (Archer et al., 2007)(Pentkowski et al., 2021). There are currently more than 55 million incidences of dementia globally, with the prevalence of the disease reaching to 10 million new cases year (World Health Organization, n.d.). The onset and progression of AD are influenced by genetic and environmental factors (Dunn, O'Connell, & Kaczorowski, 2019). Vitamin D deficiency has been suggested as a promising prognostic factor for dementia, along with other possibly risk factors for AD including a family history of Alzheimer's, being an APOE-e4 gene carrier, depression, hypertension, and diabetes (Pogge, 2015). In determining dietary vitamin D requirements, circulating 25-hydroxyvitamin D is an effective marker of vitamin D state, especially for assessing vitamin D deficiency or insufficiency (Trimboli et al., 2021). Since vitamin D is involved in neural transmission, neuroprotection, and neural plasticity, it has

been investigated that low concentration of vitamin D may assist in the progression of AD (Mayne & Burne, 2019).

Meta-analysis published in 2013, revealed statistically significant differences between patients with AD patients and control for serum 25-hydroxyvitamin D levels (Annweiler, Llewellyn, & Beauchet, 2013)(Zhao, Sun, Ji, & Shen, 2013). However, 33% (Zhao et al., 2013) and 57% (Annweiler et al., 2013) of studies that were included in an earlier meta-analysis failed to fulfil the criteria for inclusion in the present meta-analysis. Meanwhile, since then, other studies have been published (Wintzell V, Svanström H, 2022). This study specifically uses normal cognitive patients as a comparator which is a great potential method for reducing bias. The aim with this meta-analysis is to investigate quantitatively the association of serum 25-hydroxyvitamin D and Alzheimer's disease, which could get clarify the association, potential effects on the therapy and prevention of the diseases. Additionally, meta-regression was also performed to investigate the source of heterogeneity that was not addressed statistically by previous meta-analysis.

METHODS

This review is presented according to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

Eligibility criteria

The studies must fulfill these criteria in order to be considered for inclusion: (1) Target population was patients with Alzheimer's Disease; and (2) Patients with normal cognitive function was used as comparator;(3) Studies that reported 25-hydroxyvitamin D level in mean ± standard deviation values; (4) Observational studies.

Information source

Pubmed database was used to perform the literature search from inception up to November 2022.

Searching strategies

The following search term was used to find relevant articles: "Alzheimer" AND "Vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D".

Study selection

The article titles and abstracts were assessed in accordance with the inclusion criteria. A consensus must be reached during the full-text selection stage to determine which studies need to be included or excluded. Disagreements in the findings of the selected studies were resolved by discussion.

Data extraction

From eligible studies, the following information were extracted using pre-designed form: (1) Publication year; (2) Name of first author; (3) Country; (4) The number of participant; and (4) Gender; (5) The mean and standard deviation values of age; (6) The value of mean and standard deviation of 25(OH)D. The outcomes from studies which provided data in ng/dL were converted to nmol/L (the value in ng/mL was multiplied by 2.5). Additionally, WebPlotDigitizer was also used to obtain numeric data from eligible studies that present outcome in graphs.

Statistical analysis

In present meta-analysis, the continuous outcome from eligible studies were used to assess the 25-hydroxyvitamin D levels in AD patients versus normal cognitive patients. In terms of missing data, imputation was not performed. The WMD was determined with a 95% confidence interval (CI) using a random-effect model. Statistically significant difference was evaluated using a p-value ≤ 0.05 and the I^2 was used to represent statistical heterogeneity. A random-effects meta-regression was also conducted using the mean age of the participants to identify the potential source of heterogeneity. All statistical analysis was conducted using the Stata 16.0.

RESULTS

Study selection process

There were 510 potential identified articles in our database search. After removing duplicates (n = 1) and retracted articles (n = 9), 500 articles were screened manually based on title and abstract. Twenty-three were classified as relevant articles. Then, a full-text assessment was carried out for those articles resulting in 6 articles to be considered for inclusion. The selection of the studies was summarized in Fig. 1.

Study characteristics

The studies included were published between 1990 and 2021. In addition to two studies in the United State of America (Wintzell V, Svanström H, 2022)(Page et al., 2021), studies were also carried out in England (Ferrier et al., 1990), Germany (Luckhaus et al., 2009), Greece (Mavraki et al., 2020), and Turkey (Ertilav, Barcin, & Ozdem, 2021). The number of patients were range from 15 (Ferrier et al., 1990) to 138 (Mavraki et al., 2020) and all of the studies focused on elderly people (Wintzell V, Svanström H, 2022) (Page et al., 2021)(Evatt, DeLong, et al., 2008)(Buell et al., 2010)(Ferrier et al., 1990)(Luckhaus et al., 2009). Concisely, table 1 presents the baseline characteristics of the six included studies.

Serum 25-hydroxyvitamin D in AD patients

The overall analysis revealed a significant difference of 25-hydroxyvitamin D between AD and normal cognitive patients (WMD = -9.82, 95% CI = -15.09, -4.55, p = 0.00. Fig. 2). Moreover, it also indicated that levels of 25-hydroxyvitamin D in AD patients were lower compared to normal cognitive patients.

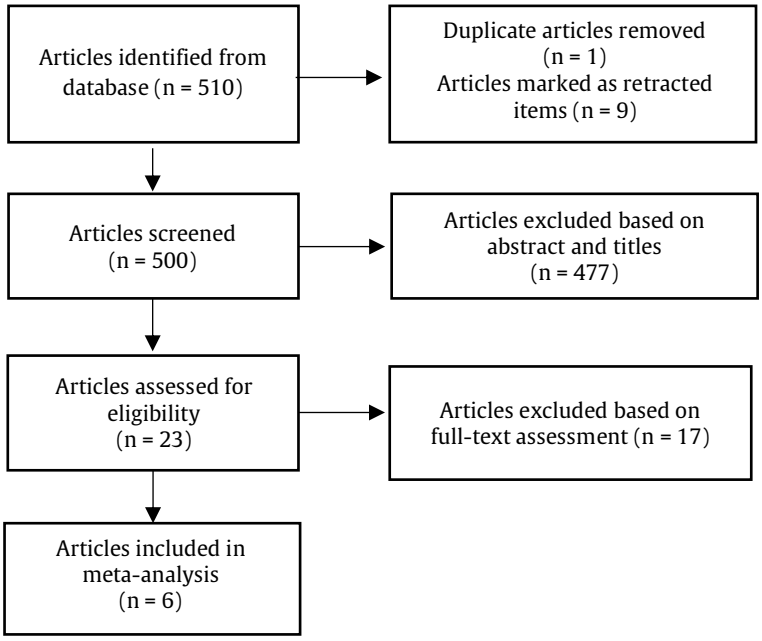

Fig. 1. PRISMA selection flow.

Fig. 1. PRISMA selection flow.

Publication	First Author	Country	N		Gender (% male)		Age (years)		25-hydroxyvitamin D levels (nmol/L)	
			AD	Control	AD	Control	AD	Control	AD	Control
1990	Ferrier (Ferrier et al., 1990)	England	15	15	-	-	76.00 ± 7.00	76.00 ± 9.00	32.00 ± 9.00	40.00 ± 25.00
2008	Evatt (Evatt, Delong, et al., 2008)	USA	97	99	57	57	66.4 (47-88)	65.7 (39-89)	86.86 ± 38.43	92.35 ± 36.19
2009	Luckhaus (Luckhaus et al., 2009)	Germany	20	8	60	50	70.35 ± 8.23	72.40 ± 6.10	39.43 ± 24.46	35.94 ± 12.97
2010	Buell (Buell et al., 2010)	USA	41	211	-	-	80.40 ± 8.00	72.50 ± 7.70	42.18 ± 15.72	49.92 ± 20.46
2020	Mavraki (Mavraki et al., 2020)	Greece	138	103	61	50	75.51 ± 6.72	74.00 ± 5.41	32.14 ± 19.16	47.34 ± 20.81
2021	Ertilav (Ertilav et al., 2021)	Turkey	85	85	41.2	52.9	75.54 (60–99)	70.16 (61–84)	41.93 ± 29.95	59.65 ± 31.69

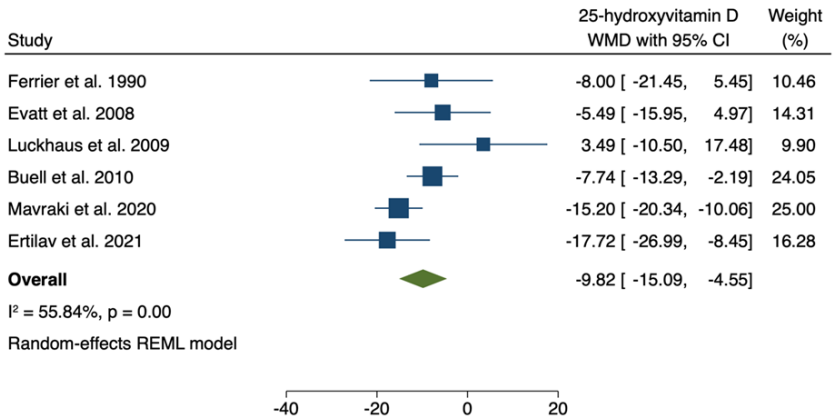

Fig. 2. Forest plot of serum 25-hydroxyvitamin D in AD

Meta-regression

In previous studies it was stated that differences in the mean age of patients could be the source of heterogeneity although no meta-regression analysis was performed (Zhao et al., 2013). In present meta-analysis, meta-regression was carried out to confirmed the previous statement. The study's findings revealed mean age was not the potential source of heterogeneity (coefficient = -0.55, 95 % CI = -2.23, 1.11, p = 0.513). Regarding the heterogeneity among studies (I^2 = 55.84%), it might be due to the differences in genetic factors, ethnicities, variation of sunshine exposure and vitamin D supplementation of the patients [24–26].

DISCUSSIONS

The present meta-analysis aimed to evaluate the association of 25-hydroxyvitamin D levels and Alzheimer's Disease. The findings found a lower levels of 25-hydroxyvitamin D in AD than in normal cognitive patients. The underlying mechanisms of vitamin D levels implications on the onset and progression of AD have not been fully established in current studies, but several possible mechanisms have been proposed. First, preclinical studies have demonstrated that low levels of vitamin D play an important role in the brain. Vitamin D deficiency can modulate Aβ clearance from the brain (Luckhaus et al., 2009). While studies on humans has also revealed diminished of Aβ in the brain modulated by vitamin D (Soares et al., 2021). Second, vitamin D has been confirmed to maintain calcium homeostasis of nerve impacted by peptide Aβ by modulating voltage-gated calcium channels, which are the target of peptide Aβ (Dursun, Gezen-Ak, & Yilmazer, 2011). Third, by promoting vitamin D receptor expression and performing as an antioxidant, vitamin D can defend against glutamate neurotoxicity (Patel & Shah, 2017).

There are several factors that affect vitamin D levels in AD patients, including genetic and environmental factors (Farag, Jomaa, El-Wahed, & El-Seedi, 2020) . In genetic factor, It has been proposed that there is a significant relationship between APOE ε4 allele and AD (Belloy, Napolioni, & Greicius, 2019). Although it is not entirely specific or sensitive, APOE ε4 is the only biological predisposition for AD that has been firmly established (Soares et al., 2021). The APOE 4 allele may contribute to the development of AD patients who initiate show symptoms of cognitive deterioration (Białecka-Dębek, Granda, Szmidt, & Zielińska, 2021).

Age is a factor that has an important effect on the levels of vitamin D (Zhao et al., 2013). Calcium malabsorption commonly occurs in individuals older than 70 years (Shlisky et al., 2022). Age-related changes in calcium absorption have been linked to abnormalities in transport proteins that act via vitamin D receptors (Aydemir, Erdogan, & Türkeli, 2021). Furthermore, lower levels of 7-dehydrocholesterol in the epidermis (Anderson et al., 2020) and a reduced response to UV are more common in the older age, thus there is a 50% decrease in the formation of previtamin D3 (Wei, Zhu, & Ji, 2019).

Ethnicity is another factor that plays a role in influencing vitamin D concentration. Vitamin D deficiency is more common among African Americans (blacks) than other Americans (Sutherland et al., 2021). Whereas risk factors for dementia, such as hypertension and diabetes, are more frequent in black and other ethnic minorities (Clark et al., 2018). Numerous studies show that people from black ethnic groups have a higher incidence of AD than people from Asian ethnic groups (Mayeda, Glymour, Quesenberry, & Whitmer, 2016).

An external factor that is commonly known to affect vitamin D levels is the duration a person is exposed to the sunlight (Elseesy et al., 2020). Since AD is a degenerative condition that leads to disabilities and functional decline, patients have trouble getting adequate sunlight exposure to generate enough vitamin D (Bivona et al., 2019). Furthermore, it could be challenging for some patients to get enough foods that are rich in vitamin D, though some patients take vitamin D supplements to reach their body's needs (Bivona et al., 2019). Moreover, dementia may lead to decreased vitamin D intake and less time spent outside activity with decreased exposure to sunlight, both of which can limit the substrate source to 25-hydroxyvitamin D (Bivona et al., 2019). This substrate deficiencies are important to identified because they can be prevented and treated (Bikle, 2014). By controlling these factors, some of the studies included strengthen the findings' reliability.

Present meta-analysis has some limitations. First, this study does not explicitly describe the duration of AD patients are exposed to sunlight per day. Second, there is no extraction of data related to the source of vitamin D derived from diet or supplementation. Third, the historical medication of AD patients is also not described.

CONCLUSIONS

This study showed that patients with AD had lower levels of 25-hydroxyvitamin D than patients with normal cognitive function. These findings suggest a potential role of vitamin D which could have effects on the prevention and therapy of AD. Further research are needed to explore and elucidate potential neuroprotective effects of vitamin D in AD.

Acknowledgements

Not applicable.

Funding

None of the above.

Consent for publication

Not applicable.

Conflicting interests

The authors declare that no commercial or financial relationships existed that could be construed as a potential conflict of interest during the research.

REFERENCES

Anderson, A., Campo, A., Fulton, E., Corwin, A., Jerome, W. G., & O'Connor, M. S. (2020). 7-Ketocholesterol in disease and aging. *Redox Biology*, *29*, 101380. https://doi.org/https://doi.org/10.1016/j.redox.2019.101380

Annweiler, C., Llewellyn, D. J., & Beauchet, O. (2013). Low serum vitamin D concentrations in Alzheimer's disease: A

systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *33*, 659–74. https://doi.org/10.3233/JAD-2012-121432

Archer, N., Brown, R. G., Reeves, S. J., Boothby, H., Nicholas, H., Foy, C., … Lovestone, S. (2007). Premorbid personality and behavioral and psychological symptoms in probable Alzheimer disease. *The American Journal of Geriatric Psychiatry*, *15*(3), 202–13. https://doi.org/https://doi.org/10.1097/01.JGP.0000232510.77213.10

Aydemir, Y., Erdogan, B., & Türkeli, A. (2021). Vitamin D deficiency negatively affects both the intestinal epithelial integrity and bone metabolism in children with Celiac disease. *Clinics and Research in Hepatology and Gastroenterology*, *45*(4), 101523. https://doi.org/https://doi.org/10.1016/j.clinre.2020.08.002

Belloy, M. E., Napolioni, V., & Greicius, M. D. (2019). A Quarter century of APOE and Alzheimer's disease: Progress to date and the path forward. *Neuron*, *101*(5), 820–38. https://doi.org/https://doi.org/10.1016/j.neuron.2019.01.056

Białecka-Dębek, A., Granda, D., Szmidt, M. K., & Zielińska, D. (2021). Gut microbiota, probiotic interventions, and cognitive function in the elderly: A review of current knowledge. *Nutrients*, *13*(8). https://doi.org/10.3390/nu13082514

Bikle, D. D. (2014). Vitamin D metabolism, mechanism of sction, and clinical spplications. *Chemistry & Biology*, *21*(3), 319–29. https://doi.org/https://doi.org/10.1016/j.chembiol.2013.12.016

Bivona, G., Lo Sasso, B., Iacolino, G., Gambino, C. M., Scazzone, C., Agnello, L., & Ciaccio, M. (2019). Standardized measurement of circulating vitamin D [25(OH)D] and its putative role as a serum biomarker in Alzheimer's disease and Parkinson's disease. *Clinica Chimica Acta*, *497*, 82–7. https://doi.org/https://doi.org/10.1016/j.cca.2019.07.022

Buell, J. S., Dawson-Hughes, B., Scott, T. M., Weiner, D. E., Dallal, G. E., Qui, W. Q., … Tucker, K. L. (2010). 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology*, *74*(1), 18–26. https://doi.org/10.1212/WNL.0b013e3181beecb7

Clark, D. G., Boan, A. D., Sims-Robinson, C., Adams, R. J., Amella, E. J., Benitez, A., … Ovbiagele, B. (2018). Differential impact of index stroke on dementia risk in African-Americans compared to whites. *Journal of Stroke and Cerebrovascular Diseases*, *27*(10), 2725–30. https://doi.org/https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.048

Cortes-Canteli, M., & Iadecola, C. (2020). Alzheimer's disease and vascular aging: JACC focus seminar. *Journal of the American College of Cardiology*, *75*(8), 942–51. https://doi.org/https://doi.org/10.1016/j.jacc.2019.10.062

Dunn, A. R., O'Connell, K. M. S., & Kaczorowski, C. C. (2019). Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease. *Neuroscience & Biobehavioral Reviews*, *103*, 73–80. https://doi.org/https://doi.org/10.1016/j.neubiorev.2019.06.018

Dursun, E., Gezen-Ak, D., & Yilmazer, S. (2011). A novel perspective for Alzheimer's disease: Vitamin D receptor suppression by amyloid-β and preventing the amyloid-β induced alterations by vitamin D in cortical neurons. *Journal of Alzheimer's Disease*, *23*(2), 207–19. https://doi.org/10.3233/JAD-2010-101377

Elseesy, S. W., Goueli, T., Mostafa, A., Afif, A., & Khalil, M. A. (2020). Relation between vitamin D level and severity, symptomatology and cognitive dysfunction of major depressive disorder–A sample of Egyptian patients. *Neurology, Psychiatry and Brain Research*, *35*, 10–5. https://doi.org/https://doi.org/10.1016/j.npbr.2019.12.001

Ertilav, E., Barcin, N. E., & Ozdem, S. (2021). Comparison of serum free and bioavailable 25-Hydroxyvitamin D Levels in Alzheimer's disease and healthy control patients. *Laboratory Medicine*, *52*(3), 219–25. https://doi.org/10.1093/labmed/lmaa066

Evatt, M. L., Delong, M. R., Khazai, N., Rosen, A., Triche, S., & Tangpricha, V. (2008). Prevalence of vitamin d insufficiency in patients with Parkinson disease and Alzheimer disease. *Archives of Neurology*, *65*(10), 1348–52. https://doi.org/10.1001/archneur.65.10.1348

Evatt, M. L., DeLong, M. R., Khazai, N., Rosen, A., Triche, S., & Tangpricha, V. (2008). Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. *Archives of Neurology*, *65*(10), 1348–52. https://doi.org/10.1001/archneur.65.10.1348

Farag, M. A., Jomaa, S. A., El-Wahed, A. A., & El-Seedi, A. H. R. (2020). The many faces of kefir fermented dairy products: Quality characteristics, flavour chemistry, nutritional value, health benefits, and safety. *Nutrients*, *12*(2), 346. https://doi.org/10.3390/nu12020346

Ferrier, I. N., Leake, A., Taylor, G. A., McKeith, I. A. N. G., Fairbairn, A. F., Robinson, C. J., … Edwardson, J. A. (1990). Reduced gastrointestinal absorption of calcium in dementia. *Age and Ageing*, *19*(6), 368–75. https://doi.org/10.1093/ageing/19.6.368

Long, J. M., & Holtzman, D. M. (2019). Alzheimer disease: An update on pathobiology and treatment strategies. *Cell*, *179*(2), 312–39. https://doi.org/https://doi.org/10.1016/j.cell.2019.09.001

Luckhaus, C., Mahabadi, B., Grass-Kapanke, B., Jänner, M., Willenberg, H., Jäger, M., … Fehsel, K. (2009). Blood biomarkers of osteoporosis in mild cognitive impairment and Alzheimer's disease. *Journal of Neural Transmission*, *116*(7), 905–11. https://doi.org/10.1007/s00702-009-0241-x

Mavraki, E., Ioannidis, P., Tripsianis, G., Gioka, T., Kolousi, M., & Vadikolias, K. (2020). Vitamin D in mild cognitive impairment and Alzheimer's disease. A study in older Greek adults. *Hippokratia*, *24*(3), 120–6. Retrieved from https://pubmed.ncbi.nlm.nih.gov/34239289

Mayeda, E. R., Glymour, M. M., Quesenberry, C. P., & Whitmer, R. A. (2016). Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimer's & Dementia*, *12*(3), 216–24. https://doi.org/https://doi.org/10.1016/j.jalz.2015.12.007

Mayne, P. E., & Burne, T. H. J. (2019). Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness. *Trends in Neurosciences*, *42*(4), 293–306. https://doi.org/https://doi.org/10.1016/j.tins.2019.01.003

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews*, *10*(1), 89. https://doi.org/10.1186/s13643-021-01626-4

Patel, P., & Shah, J. (2017). Role of vitamin D in Amyloid clearance via LRP-1 upregulation in Alzheimer's disease: A potential therapeutic target? *Journal of Chemical Neuroanatomy*, *85*, 36–42.

https://doi.org/https://doi.org/10.1016/j.jchemneu.2017.06.007

Pentkowski, N. S., Rogge-Obando, K. K., Donaldson, T. N., Bouquin, S. J., & Clark, B. J. (2021). Anxiety and Alzheimer's disease: Behavioral analysis and neural basis in rodent models of Alzheimer's-related neuropathology. *Neuroscience & Biobehavioral Reviews*, *127*, 647–58. https://doi.org/https://doi.org/10.1016/j.neubiorev.2021.05.005

Pogge, E. (2015). *Vitamin D in synaptic plasticity, cognitive function, and neuropsychiatric illness* (R. R. Watson & V. R. B. T.-B. N. and D. S. in N. and B. D. Preedy, eds.). https://doi.org/https://doi.org/10.1016/B978-0-12-411462-3.00049-7

Shlisky, J., Mandlik, R., Askari, S., Abrams, S., Belizan, J. M., Bourassa, M. W., … Weaver, C. (2022). Calcium deficiency worldwide: prevalence of inadequate intakes and associated health outcomes. *Annals of the New York Academy of Sciences*, *1512*(1), 10–28. https://doi.org/10.1111/nyas.14758

Soares, J. Z., Pettersen, R., Benth, J. š., Persson, K., Strobel, C., Selbæk, G., & Bogdanovic, N. (2021). Vitamin D Levels, APOE Allele, and MRI volumetry assessed by NeuroQuant in Norwegian adults with cognitive symptoms. *Journal of Alzheimer's Disease*, *79*, 311–21. https://doi.org/10.3233/JAD-201018

Sutherland, J. P., Zhou, A., Leach, M. J., & Hyppönen, E. (2021). Differences and determinants of vitamin D deficiency among UK biobank participants: A cross-ethnic and socioeconomic study. *Clinical Nutrition*, *40*(5), 3436–47. https://doi.org/https://doi.org/10.1016/j.clnu.2020.11.019

Trimboli, F., Rotundo, S., Armili, S., Mimmi, S., Lucia, F., Montenegro, N., … Angotti, E. (2021). Serum 25-hydroxyvitamin D measurement: Comparative evaluation of three automated immunoassays. *Practical Laboratory Medicine*, *26*, e00251. https://doi.org/https://doi.org/10.1016/j.plabm.2021.e00251

Wei, J., Zhu, A., & Ji, J. S. (2019). A comparison study of vitamin D deficiency among older adults in China and the United States. *Scientific Reports*, *9*(1), 19713. https://doi.org/10.1038/s41598-019-56297-y

Wintzell V, Svanström H, P. B. (2022). Selection of comparator group in observational drug safety studies: Alternatives to the active comparator new user design. *Epidemiology*, *33*(5), 707–14. https://doi.org/10.1097/EDE.0000000000001521

World Health Organization. (n.d.). Dementia. Retrieved October 2, 2022, from https://www.who.int/news-room/fact-sheets/detail/dementia

Zhao, Y., Sun, Y., Ji, H.-F., & Shen, L. (2013). Vitamin D levels in Alzheimer's and Parkinson's diseases: A meta-analysis. *Nutrition*, *29*(6), 828–32. https://doi.org/https://doi.org/10.1016/j.nut.2012.11.018